In the Drawing:

A replacement sheet for the first sheet of the drawing accompanies this amendment. Changes were required on figure 1 to correctly indicate the length of the androgen receptor fragment, which includes amino acids 325 to 918 of the human androgen receptor of SEQ ID NO: 8. Approval of the changes in figure 1 is respectfully requested.

In the Sequence Listing:

Please accept the accompanying written sequence listing section, which is a replacement section that replaces the previously filed written sequence listing section. The accompanying written sequence listing section includes a new sequence, SEQ ID NO: 8, for the human androgen receptor protein of Genbank AAA51775, which is used in the experiments described on pages 17 to 21 of applicants' originally filed specification. The accompanying written sequence listing section includes the same amino acid sequence as deposited in Genbank AAA51775. No changes were made in the other sequences, SEQ ID NO: 1 to SEQ ID NO: 7, in the accompanying written sequence listing section. Thus the accompanying written sequence listing with SEQ ID NO: 8 is **not** new matter.

Furthermore a 3 1/2" floppy disk has been filed with the accompanying written sequence in computer readable form (CRF). It is warranted that the sequence listing in the CRF on the floppy disk is the same as the accompanying written sequence listing and that no new matter has been added via the floppy disk.

REMARKS

I. PRIORITY

Applicants fully appreciate the necessity of filing a certified English translation of U.S. Provisional Application 60/465,692 in order to receive the benefit of the earlier filing date based on this provisional application and to provide a basis for the cross-reference added to the specification.

A certified English translation of U.S. Provisional Application 60/465,692 accompanies this amendment. The English translation of the US Provisional Application Ser. No. 60/465,692 will show that the claims are fully supported by the disclosures in the provisional application.

II. SPECIFICATION, SEQUENCE LISTING AND DRAWING

The submission of the English translation of the provisional application, which was discussed above, should overcome the objection to the disclosure based on its absence.

The specification has been amended to delete the first page with the "extraneous matter", which is recommended by Rule 77 b if the data is not included in the application data sheets. However the data was supplied on the application data sheets so it has been deleted. The title of the invention has been moved to the page numbered 2 originally, which is now the first page of the

specification. It is followed by the appropriate cross-reference, which will be supported by the certified English translation of the provisional application.

The description of figures 5a and 5b in the "Brief Description of the Drawing" is believed to be correct. These figures show the distributions of the EWS transcripts and AR transcripts respectively. However the normal expression of these proteins in the respective tissues can be ascertained from the figures showing the distribution of these transcripts in them.

The last three paragraphs of the "Detailed Description" section have been amended with the foregoing understanding in mind. The subject matter in these paragraphs unfortunately became "mixed up" and needed some substantial changes. The sentence on page 21, lines 12 to 16, refers to fig. 5b, not fig. 5a and has been deleted. The subject matter on page 21, lines 16 to 23, was a partial repeat of the subject matter in the last paragraph on page 22, which is relevant to fig. 5a. Some subject matter from the last paragraph on page 22 has been added to the paragraph on page 21 and the last paragraph on page 22 was then deleted to avoid needless repetition.

The two paragraphs describing figs. 5a and 5b have been amended to make it clear that figures 5a and 5b show distributions of protein transcripts in tissues.

The reference to the androgen receptor binding domain on page 16 in relation to figure 2 was indeed incorrect. The correct region is 319 to 656 and the reference on page 16 has been amended accordingly.

The correct length of the human androgen receptor fragment is AS 325 to

AS 918. The description of figure 1 on page 16 has been amended accordingly. Figure 1 itself required correction to state that the fragment includes amino acids 325 to 918 of the androgen receptor, as indicated above.

A replacement sequence listing section including the amino acid sequence for human androgen receptor (SEQ ID NO: 8) accompanies this amendment as required by the Office Action. As noted above, the addition of this new sequence listing to the specification does **not** add new matter because it is described by reference to its Genbank Access number AAA51775 on pages17 to 25 of the originally filed specification in accordance with 37 C.F.R. 1.825. The replacement sequence listing on the accompanying floppy disk is identical with the written replacement sequence listing accompanying this amendment and is warranted not to add new matter in accordance with 37 C.F.R. 1.825.

III. INDEFINITENESS REJECTION AND CLAIM OBJECTIONS

Claims 3 to 8 and 31 were rejected under 35 U.S.C. 112, second paragraph, for indefiniteness.

Claims 3 and 6 have been amended to correct the error in the length of the amino acid sequence for human androgen receptor, which has crept into the amended claims due to typographical errors in the disclosure in the specification. Similar changes have been made in the description of the drawing figures in the specification. It is indeed true that the last amino acid in the amino acid sequence of the human androgen receptor at Genbank AAA51775 (SEQ ID NO: 8) is

amino acid No. 918. The claims and disclosure have been accordingly amended.

Furthermore the particular human androgen receptor protein with the amino acid sequence of Genbank AAA51775 used in the examples has been included in new dependent claims 32 and 33 as SEQ ID NO: 8. These claims depend on claims 3 and 6 respectively, however claims 3 and 6 have not been limited to the particular human androgen receptor protein amino acid sequence specified by SEQ ID NO: 8. The same is true of new claims 34 and 35.

The term "hormonal effect" has been replaced by the term "androgen or anti-androgen effect". The methods for testing substances described in the claims were limited to testing for substances that modulate or change the interaction between EWS co-modulator and human androgen receptor or a fragment thereof as defined in the claims. Thus the hormonal effects would be those associated with androgen receptor, namely androgen or anti-androgen effects. Basis for this change is provided in the specification at various points, but particularly see page 11, line 19 to page 12, line 5; page 13, line 20 to page 14, line 5, and page 9, lines 18 to 22.

Claim 6 has been amended to correct the typographical errors, "transfixed" has been changed to "transfected".

Claim 31 has been amended to change "and/or" to "or". Each of the recited biotechnology methods of measuring interactions can be employed separately, which is supported by the disclosure on page 10, lines 12 to 17.

The misspellings in claims 5 and 8 have been corrected.

For the foregoing reasons and because of the changes in claims 3 to 8

and 31, withdrawal of the rejection of amended claims 3 to 8 and 31 under 35 U.S.C. 112, second paragraph, for indefiniteness is respectfully requested.

Similarly the withdrawal of the objection to claims 5 and 8 because of the typographical errors is requested on the basis of the changes made in the amended claims 5 and 8.

IV. REJECTION OF CLAIMS FOR LACK OF AN ENABLING DISCLOSURE

Claims 3 to 8 and 31 were rejected under 35 U.S.C. 112, first paragraph, because these claims were found to be too broad in their scope to be enabled by the originally filed specification with the examples present in the specification.

A. New Claims 34 and 35

However page 6 of the Office Action found that the originally filed specification was enabling for the method of screening test compounds when performed with the full-length EWS protein of SEQ ID NO: 2 and the full-length human androgen receptor. Accordingly new claims 34 and 35 corresponding to the broader claims 6 and 3 respectively are added above. Claims 34 and 35 are limited to the full-length EWS protein of SEQ ID NO: 2 and the full-length human androgen receptor.

For the foregoing reasons the allowance of claims 34 and 35 is respectfully solicited. These claims should not be rejected under 35 U.S.C. 112, first paragraph.

B. Claims 3 to 8 and 31

However it is respectfully submitted that the rejection of claims 3 and 6 under 35 USC 112, first paragraph, and of course of claims 3 to 8 and 31, should be withdrawn.

First note that screening method claims 3 and 6 are limited to the fragment of AR comprising AS 325 to 918 and the fragment of EWS with AS 319 to 656. In other words, the amino acid sequence of each fragment is limited to a single sequence in the case of each protein.

Applicants' have proven experimentally that the particular claimed fragments of EWS and AR bind to each other by means of the yeast two-hybrid assay described in the specification (Page 18, line 12, to page 20, line 5) when no test substance is present. Since the binding can be measured or detected, for example by the yeast two-hybrid assay, then the effect of an added test substance on the binding is easy to determine. One simply measures or performs the yeast two-hybrid assay first without the test substance present as a control and then later performs it again under the same conditions except that the test substance is present. If there is no difference in the test results, then the test substance had no effect on the binding of the particular EWS fragment with the particular AR fragment under the test conditions.

The proposed test is a screening test that can be used to test a large number of different test substances. To be sure there are some uncertainties associated such screening tests in general, but a strong positive result regarding the effect of a test substance on the interaction provides a strong reason for

further investigation, perhaps including clinical tests. That is what is meant by a "screening" test.

On the other hand, the present specification (pages 18 and 19) is clearly enabling for the case of the broad claim 3 (which covers the fragments as well as the full-length proteins) because of the description of the two-hybrid yeast screen carried out with the EWS fragment and the AR2 fragment, which contains AS 325 - 918 of the AR, which is described on pages 18 to 19 of applicants' specification. The C-terminal AR fragment, which substantially does not include the AR region from AS 141 to 338 described by Heinlein, et al, and mentioned in the Office Action, was found to sufficient to bind by itself to the identified EWS fragment in the applicants' experiments. The binding was confirmed by comparison with the yeast two-hybrid control experiment as described on page 19, lines 9 to 11. The result is summarized again in the disclosure from page 19, last line, to page 20, lines 1 to 2.

The fact that the fragment of a C-terminal region of AR, which does not contain the sequences AS 141 to 338 of AR, is sufficient to interact with the EWS protein in the yeast two-hybrid assay is consistent with other result from the literature. An Information Disclosure Statement with seven references, including those from the Chang laboratory accompanies this amendment. These references show that the C-terminal region of AR can interact by itself with other proteins. One reason for this is that the LBD binding domain, which is part of this fragment, is necessary for ligand binding, for example for transcription.

Of course proteins might also bind with the N-terminal fragment of AR,

which is not part of the C-terminal region, but the ligand dependency of the interaction would then be missing since the LBD region is missing.

Analogous to the assays described in the seven articles filed with the Information Disclosure Statement, one skilled in the art may provide an assay using a fragment of AR which substantially does not contain amino acids 141 to 338, as long as it is known that the protein interacting with the AR interacts with the aforesaid C-terminal region of the AR or with the AR fragment including AS 325 to 918. The experimental results in the specification show that the EWS fragment of claim 3 does bind with the AR fragment of claim 3.

In addition, considering the extraordinarily long time periods required to develop acceptable medications for treating diseases and conditions and the importance of these treatments to patients, secondary utilitarian considerations warrant the granting of patents for screening tests that reduce the effort and expense of developing such medications.

For the foregoing reasons withdrawal of the rejection of amended claims 3 to 8 and 31 under 35 U.S.C. 112, first paragraph, for lack of enablement is respectfully requested.

Furthermore it is respectfully submitted that none of the new claims 32 to 35 should rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put

this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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